Cardiomyopathies and heart failure

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Abstract

Primary heart failure in cardiomyopathy occurs in (1) hypertrophic cardiomyopathy, a genetic disease of the sarcomere; and (2) in dilated cardiomyopathy. The latter is often regarded as idiopathic in origin, but requires exclusion of all possible etiologies which are becoming easier to identify with modern investigative techniques. Tachycardia-induced cardiomyopathy is now increasingly recognized especially in uncontrolled atrial fibrillation. Pharmacological treatment of cardiomyopathic heart failure includes diuretics, renin-angiotensin-aldosterone inhibition (RAAS), β-blockade, vasodilators and metabolic therapy. Agents that modify fatty acid metabolism such as trimetazidine and perhexiline and ranolazine can have beneficial effects. In addition, in one study trimetazidine unexpectedly increased high-density lipoprotein-cholesterol (HDL-C).
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"A big heart is bad heart." Interpretation of the Egyptian Book of the Dead

Introduction

The term ''cardiomyopathy'' literally means ''disease of the heart muscle'' (myopathy, muscle degeneration). In practice, this term specifically means a primary disease of the heart muscle of unknown causation, which may present as heart failure. Of particular interest are two groups of such diseases: those that are genetically determined, such as hypertrophic cardiomyopathy, and those that are of unknown origin, the idiopathic dilated cardiomyopathy (DCM) group. These two extremes are morphologically very different (*Figure 1*). In the cardiomyopathy group, of specific therapeutic interest is the use of metabolically active agents such as trimetazidine that favorably influence muscle metabolism and lead to clinical improvements.

Primary myocardial failure in cardiomyopathy

In primary myocardial failure, there is no initial defect in the loading conditions of the left ventricle, so that both volume and pressure load are initially normal. For a given end-diastolic volume (and, therefore, sarcomere length), tension generation is inadequate as a result of the primary myocardial disease or cardiomyopathy. Sometimes the cause of the disease is known (secondary cardiomyopathy), and sometimes it is unknown (primary cardiomyopathy). For practical purposes, whenever the origin of the myocardial disease is obscure, it is useful to think of a state of primary cardiomyopathy.

Hypertrophic cardiomyopathy

In hypertrophic cardiomyopathy, the ventricular wall is abnormally thick and the cavity size small (*Figure 1b*). There are some similarities between the early stages of compensated concentric hypertrophy of this type of

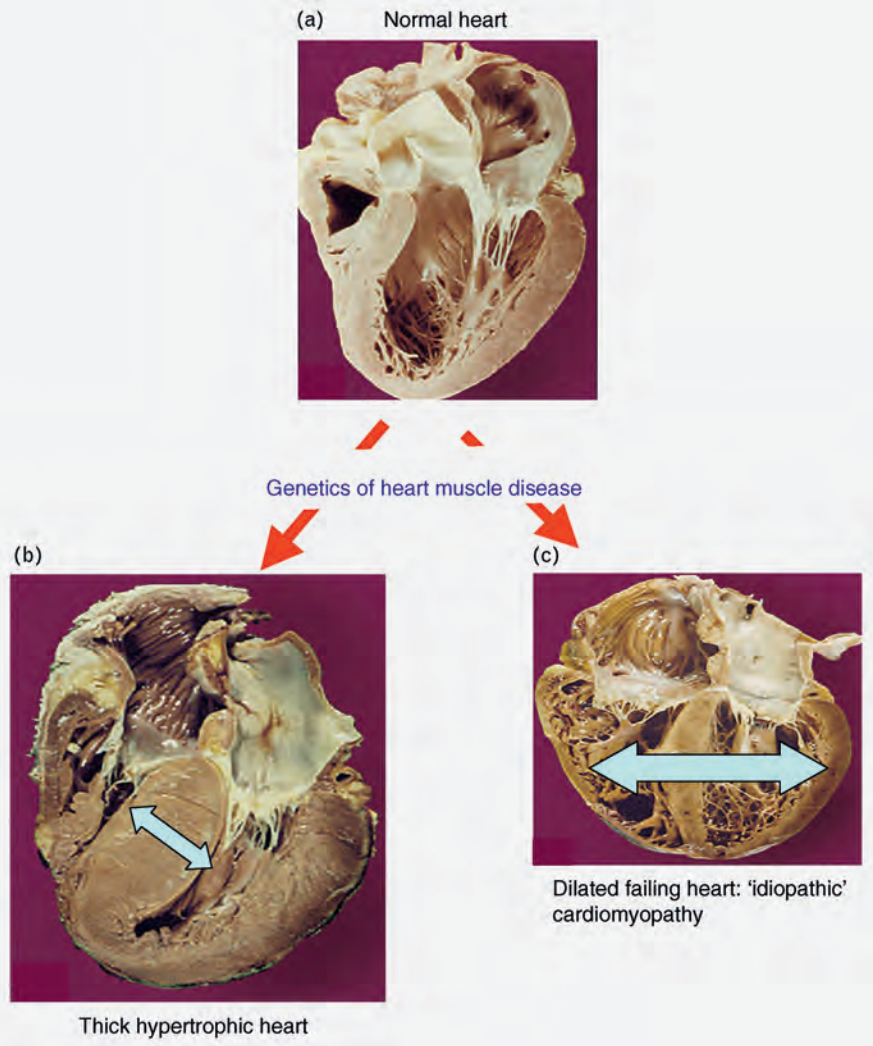

Figure 1. Patterns of cardiomyopathy. A normal heart (a) compared with the typical contrasting differences in the phenotypes of the two major types of cardiomyopathy: hypertrophic cardiomyopathy (b) and dilated cardiomyopathy (c).

cardiomyopathy and the first phase of hypertrophy in response to a pressure load. The state of marked concentric hypertrophy found in primary hypertrophic cardiomyopathy causes a high systolic ejection fraction, and diastolic dysfunction predominates. Here the major problem lies in the small size of the left ventricular cavity, which is virtually obliterated by the hypertrophy, with consequent inability to fill normally during diastole. The obstructive subvariety of hypertrophic cardiomyopathy, *hypertrophic obstructive cardiomyopathy*, is characterized by an excessively thick interventricular septum that, during systole, actually obstructs the left ventricular outflow, causing a pressure gradient between the left ventricular cavity and the aorta, thereby increasing the pressure that has to be generated within the left ventricle [1]. Thus the systolic wall stress increases, theoretically to exaggerate the degree of hypertrophy.

Genetic defects are believed to underlie hypertrophic cardiomyopathy, which is now called a ''disease of the sarcomere''. The muscle cells undergo excess growth in size in response to a genetic abnormality of the contractile proteins. The growth factors concerned may be similar to those evoked in aortic stenosis. Many abnormal genes have now been found, encoding for different contractile proteins such as β-myosin heavy chain, α-tropomyosin, or cardiac troponin T [2]. However, there is no clear correlation between the myofilament mutation and the clinical phenotype [3]. In the familial disease, there are links to mutations in the genes for AMP-activated protein kinase (AMP kinase), a key enzyme in the control of ATP concentrations in the heart. Thus the suggestion is that energy depletion may underlie the myocardial dysfunction [2]. Of interest, some of the affected patients also suffer from an inborn conduction defect called pre-excitation – that is, the Wolff–Parkinson–White syndrome. The latter may account for the high incidence of sudden death.

Table I. Causes of cardiomyopathy.

1. Primary myocardial disease	Hypertrophic (non obstructive) cardiomyopathy
	Hypertrophic obstructive cardiomyopathy
	''Idiopathic'' dilated cardiomyopathy
2. Secondary cardiomyopathy	Myocardial infarction, chronic stage
	Infective or toxic diseases (ethanol, nutritional defects, pheochromocytoma, anticancer drugs, virus myocarditis, immune mechanisms)
	Endocrine disorders
	Peripartum cardiomyopathy
	Endomyocardial fibrosis

Dilated cardiomyopathy

The hallmarks of DCM are left ventricular enlargement with wall thinning (*Figure 1c*), poor systolic function, decreased ejection fraction and cardiac output, and increased end-systolic and end-diastolic volumes. Poor systolic pressure generation causes the ejection fraction to decrease, leading to a self-induced volume overload that is accompanied by a marked increase in wall stress. There is usually a certain degree of compensatory hypertrophy, inadequate to normalize wall stress. DCM can also develop as a secondary phenomenon, whenever a large mass of myocardium is damaged, as in alcoholic damage, after a large myocardial infarct, or with severe generalized coronary artery disease (*Table I*).

Paradoxically, suspected preceding *virus infection* of the myocardium is still sometimes included in the category of idiopathic DCM, because it can act on the same cytoskeletal protein as the genetic variety, namely dystrophin. Thus a virus infection that might be occult could elicit a macrophage response that produces cytokines, which then initiate an immune response that damages the cytoskeleton [4] (*Figure 2*). There might be lymphocytic infiltrates betraying the infective origin, but if the inflammatory response is muted, the patient could present with an apparently ''idiopathic'' cardiomyopathy.

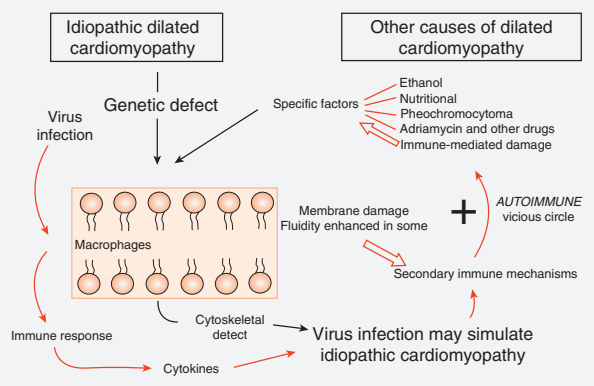

Figure 2. Postulated cellular mechanisms in dilated cardiomyopathy (DCM). Note overlap between idiopathic DCM and DCM secondary to a variety of causes. (Figure copyright L. H. Opie © 2010.).

Dystrophin is a large intracellular molecule that links actin to the sarcolemma and thence to the extracellular matrix, thereby stabilizing the sarcomeres. Dystrophin abnormalities may underlie both secondary and primary DCM. Other cytoskeleton proteins that may be associated with DCM are: (1) *desmin,* which links the Z lines and intercalated discs and their attachments to the sarcolemma; (2) the muscle LIM protein (MLP) that is part of the Z-disk–titin complex; and (3) *αB-crystallin protein*, a chaperone molecule that guards protein folding. Disruption of cytoskeletal integrity could be a feature common to both hereditary and acquired forms of DCM. More recently and more confusingly, defects in the sarcomere proteins, such as those in myosin heavy chain and troponin, have also been found in DCM, so that the molecular distinction (but not the major clinical difference) between this entity and hypertrophic cardiomyopathy seems to be blurring.

Idiopathic dilated cardiomyopathy

In idiopathic DCM, the initial event is myocardial failure of unknown cause. That means that a primary cause must be excluded, which is not a simple matter. As investigations become increasingly more sophisticated and molecular in nature, the prophesy is that an exact diagnosis will be made in about 75% of cases (*Table II*). Increasingly, abnormalities of the cytoskeleton are regarded as basic in DCM. For example, *dystrophin defects* are common. Similar dystrophin defects are found in Duchenne's genetically caused cardiomyopathy. Closely related is *dystroglycan*, an extracellular matrix protein. In animal models, defects in dystroglycan do not directly cause a cardiomyopathy, but can promote the spread of muscle damage – for example, that caused by severe exercise or by excessive β-adrenergic stimulation [5].

Cardiomyopathy of the elderly

Cardiomyopathy of the elderly is essentially the result of a decrease in the complement of myocytes (sarcopenia). From a starting point of about 10^9 cells in the heart of a young adult, the number of cells diminishes at the rate of 38×10^6 per year [6]. In compensation,

Table II. Approach to patients with suspected idiopathic cardiomyopathy. (Courtesy of Professor Bongani Mayosi.)

1. A complete and detailed family history is the cornerstone on the management of patients with cardiomyopathy
2. Idiopathic dilated cardiomyopathy (DCM) is a diagnosis of exclusion that should be made only after exhaustive non invasive and invasive investigations to rule out potentially reversible causes of heart failure
3. Clinical screening should be offered to all first-degree relatives (ie, parents, siblings, and children) of patients with hypertrophic cardiomyopathy and idiopathic DCM
4. A much lower diagnostic threshold is appropriate when interpreting diagnostic tests in first-degree relatives of patients affected with hypertrophic cardiomyopathy and unexplained DCM. In particular, there should be careful examination of the electrocardiogram and the echocardiogram for subtle abnormalities in these patients
5. The three-stage (non invasive evaluation; invasive testing; genetic testing) approach to diagnostic evaluation of unexplained DCM identifies a cause in up to 75% of cases
6. The era of molecular medicine promises to banish the diagnosis of ''idiopathic cardiomyopathy'' for good

there is modest hypertrophy of the remaining cells; however, this is unable to maintain a normal myocardial mass. Therefore there is overall loss of contractile power, accounting for the impaired effort tolerance of the elderly. Also contributing to exertional dyspnea is a decreased myocardial compliance, with diastolic heart failure.

Tachycardia-induced cardiomyopathy

Tachycardiomyopathy is the type of heart failure that is induced in animals by prolonged pacing-precipitated tachycardia. In a dog model of chronic heart failure by rapid pacing-induced tachycardia, as the plasma norepinephrine (noradrenaline) concentration increased, so did that of plasma free fatty acids (FFAs), insulin, and glucose, indicating the adrenergically induced development of insulin resistance [7]. Furthermore, in the same model, treatment by combined α- and β-blockade (carvedilol) was superior to pure β-blockade (metoprolol), showing that metabolic control, for example by β-blockade, was not enough to provide complete therapeutic relief [8]. Interestingly, in this model, a role for decreasing the concentrations of fatty acids – for example by insulin therapy – has not yet been reported.

The human counterpart is a failing heart resulting from incessant ventricular tachycardia or persistent fast atrial fibrillation. For example, in patients with atrial fibrillation without overt failure resulting from mitral valve disease in whom tachycardia-induced heart failure was suspected, the size of the left ventricle was smaller than those in the dilated hearts of patients with idiopathic cardiomyopathy and heart failure [9]. The mechanisms of the heart failure are not fully understood, but include calcium overload, ultrastructural changes such as a decreased myocyte volume, and impaired contraction of isolated myocytes.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is characterized by a ''stiff'' myocardium, which impairs diastolic relaxation and ventricular filling. The genotype is still under study. Unexpectedly, a single mutation of troponin I could, among members of the same family, cause either restrictive or hypertrophic cardiomyopathy, providing another example of overlap of clinical phenotypes associated with the same molecular genotype.

Cardiomyopathies of Africa

Heart failure of unknown origin is common in Africa, and is under intense investigation [10,11]. Two specific types are peripartum cardiomyopathy [12] and endomyocardial fibrosis [11]. Unfortunately, cardiomyopathies secondary to nutritional deficiency and alcohol abuse remain common [10].

Principles of treatment for congestive heart failure

The same principles apply to the treatment of heart failure caused by DCM as apply to that caused by other conditions.

Pharmacological treatment

Pharmacological treatment of congestive heart failure comprises five major principles.

1. *Diuretic treatment*, by increasing the output of urine and sodium, relieves the fluid retention and pulmonary congestion, thereby reducing the preload on the heart. Unfortunately, diuretic therapy promotes the secretion of renin, which helps to cause angiotensin-induced vasoconstriction. Diuretics are therefore not given indiscriminately, but are given specifically to reduce symptoms. There are no good data to show that they alter the course of events in heart failure.
2. *Inhibition of the overactive renin–angiotensin–aldosterone-system* is required. Angiotensin-converting enzyme (ACE) inhibition has several benefits. Most obviously, it relieves the vasoconstriction and excess afterload resulting from excess activation of the renin–angiotensin system. More hidden benefits might lie in the inhibition of the myocardial renin–angiotensin system and lessening of fibrosis, with improvement of diastolic function. These compounds improve exercise capacity,

probably in part through improving diastolic properties. In patients with severe congestive heart failure, added treatment with ACE inhibition decreases mortality. Treatment with angiotensin receptor blockers has generally been less successful in reducing mortality, perhaps because of underdosing, as shown by the much improved endpoint benefits in the HEAAL study that compared losartan 150 mg daily with 50 mg daily [13].

3. *β-Blockade*, cautiously introduced to those already treated as above, lessens mortality. The mechanism may be in part antiarrhythmic, in part reversed remodeling, and in part improved internal calcium cycling. Which β-blocker should be chosen? As enhanced adrenergic activity increases both α- and β-adrenergic outflow, a combined receptor blocker such as carvedilol is usually chosen, especially because, in its favor, it has better outcome data than the pure β-blockers.
4. *Vasodilators* other than ACE inhibitors, such as nitrate–hydralazine were shown to reduce mortality from heart failure when added to pre-existing treatment in patients with heart failure [14]. To date, the only convincing data have been for African-Americans; however, these drugs may be effective when added to treatment given to other patients judged to require a decrease in preload (by dilating the venous system) and a decrease in afterload (by acting as arterial dilators).
5. *Metabolic therapy* (considered below) is coming to the fore as an increasingly well documented concept.

Less used treatments

Inotropic agents

The chronic use of positive inotropic agents, including digoxin, in the treatment of congestive failure is associated with short-term stimulation of the myocardium, moving it to a higher Frank–Starling curve [15]. The use of such agents has not led to a decrease in mortality; rather, in general, they have lessened survival, perhaps because of the adverse effects of an increased cytosolic concentration of calcium. Note that there has been no well controlled study on digoxin in the modern era, whereas excellent current evidence exists for non inotropic therapy. In practice, the prescription of digoxin is declining; positive inotropes tend instead to be reserved largely for acute heart failure, for the treatment of which levosimendan is a calcium-sensitizing agent that compares well with dobutamine [16].

Gene therapy

Gene therapy is rapidly being developed. For example, fibroblasts made ''human'' by reprogramming with human ''stemness'' factors improve cytostructure and contractile function when given experimentally to infarcted hearts [17]. The drawback is that these cells must be given intramyocardially.

Cardiac resynchronization therapy

The benefits of cardiac resynchronization therapy (CRT) for patients with heart failure and with a wide QRS complex are well established, including decreased mortality. Surprisingly, there are also short-term hemodynamic effects of CRT in patients with heart failure and a narrow QRS duration, and without ventricular dyssynchrony [18]. One proposed mechanism might be through resensitization of the downregulated β-adrenergic receptor in response to chronic β-adrenergic stimulation, as found in advanced heart failure (*Figure 3*) [19].

Surgical procedures

Surgical procedures have expanded the possibilities of survival in severe heart failure. The first and best known major advance was the initial *cardiac transplantation* in Cape Town by Christiaan Barnard in 1967. This technique is still limited by problems of immune-based rejection of the donor heart, and currently by lack of donors. *Left ventricular assist devices* unload the dilated ventricle by pumping blood from the ventricle to the aorta; myocyte function and size improve, there is better uptake of calcium by the sarcoplasmic reticulum, and left ventricular remodeling is reversed. Collagen crosslinking improves,

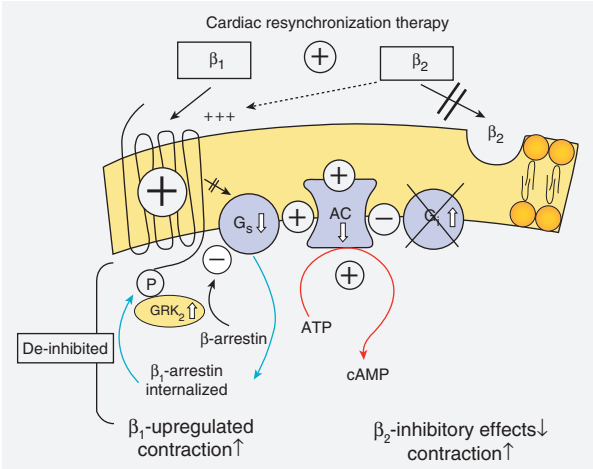

Figure 3. Cardiac resynchronization therapy (CRT) counters β-receptor downregulation. When the performance of the failing canine heart is enhanced by CRT, the adverse downregulation of the β-adrenergic receptor is countered. This constitutes proof of links between β-receptor downregulation and poor mechanical myocardial function. AC, adenylyl cyclase; GRK_2, G-protein receptor kinase-2; G_i, inhibitory G protein; G_S, stimulatory G protein. (For data, see Chakir et al [19]. Figure copyright L. H. Opie © 2010.).

suggesting decreased destruction of the extracellular matrix by matrix metalloproteinases. Thus mechanical assistance to the ailing left ventricle allows it to recover towards normal as the load is lessened, thereby providing a bridge to recovery.

Metabolic therapy for cardiomyopathy with heart failure

It is widely accepted that chronic heart failure invokes increased activity of the adrenergic system, with enhanced circulating concentrations of both epinephrine (adrenaline) and norepinephrine (noradrenaline), thus stimulating both α- and β-adrenergic receptors, with the risk of β-receptor downregulation and decreased, rather than increased, inotropic activity (for review see [20]).

Less widely, heart failure is considered to be an abnormal and adverse metabolic state in which increased FFA concentrations inhibit glucose oxidation, with the risk of insulin resistance [21,22]. Chronic inhibition of glucose oxidation by FFAs was first described in the isolated rat heart in 1961 by a Harvard group [23], and has since been confirmed in human studies. Opie and Knuuti [24] have proposed that the FFA-induced damage is widespread, and includes mitochondrial uncoupling associated with the generation of excess reactive oxygen species. The subsequent degree of oxygen wastage varies with the experimental conditions, but can be substantial, including values greater than 50% in some experiments. In this context, the therapeutic aims of metabolic therapy are: (1) to inhibit lipotoxicity and glucotoxicity, and (2) to increase glucose uptake by muscle.

Trimetazidine for heart failure

Trimetazidine is best known as an antianginal agent that is very well tolerated and is widely used in Europe. The major proposed site of action is partial inhibition of fatty acid oxidation in the heart, but many other metabolic effects have been reported. We noted that all previous studies in which trimetazidine had been evaluated as an established anti-ischemic agent in heart failure had either focused on patients with ischemic heart failure or included a majority of patients with that disease [24,25]. Thus the effects mitigating against heart failure, such as an increased ejection fraction, could have been the result of relief of ischemia, with a subsequent improvement in the glucose metabolism of the heart. We noted that decreased fatty acid oxidation of the heart was often held to be the explanation for the beneficial effects of trimetazidine in heart failure, and that the drug was effective in seven studies of heart failure, but that there had been no studies in which the rate of myocardial fatty acid oxidation had actually been measured. To date, our study has been the only one to undertake direct measurement of FFA oxidation by the heart, and the first to study chronic DCM heart failure in patients who had tested negative for myocardial ischemia [24,25].

Extracardiac effects of trimetazidine

We gave trimetazidine orally, 35 mg twice daily, and found a modest increase in the ejection fraction, from 30.9 to 34.8% ($P = 0.027$) – with, however, an unchanged myocardial fatty acid uptake and a small decrease (10%) in the rate of myocardial oxidation of FFA. We proposed that the myocardium was probably not the major site of action of trimetazidine, especially as work efficiency remained unchanged and therefore there was no effect on any FFA-induced wastage of oxygen. Trimetazidine decreased insulin resistance (glucose decreased from 5.9 ± 0.7 mmol/L to 5.5 ± 0.6 mmol/L, $P = 0.047$; insulin decreased from 10 ± 6.9 mU/L to 7.6 ± 3.6 mU/L, $P = 0.031$; homeostasis model assessment index decreased from 2.75 ± 2.28 to 1.89 ± 1.06, $P = 0.027$). Unexpectedly, plasma concentrations of high-density lipoprotein increased by 11%, presumably reflecting decreased insulin resistance. The decrease in insulin resistance confirmed previous findings in patients with diabetic heart failure; of importance, it is an independent risk factor for mortality in heart failure. We speculated that these extracardiac effects could be related, at least in part, to decreased FFA oxidation and increased glucose oxidation in skeletal muscle, as has been documented in patients with type 2 diabetes and heart failure [26].

We also noted that the change in ejection fraction induced by trimetazidine was highly correlated with β_1-receptor occupancy, suggesting a synergistic interaction between the general metabolic changes achieved by trimetazidine and the degree of β_1-receptor blockade that was already part of the existing optimal treatment of heart failure in our study. We noted that both β-blockade and trimetazidine improved insulin resistance in heart failure, and postulated that different mechanisms were operative. Hypothetically, decreased FFA oxidation and insulin resistance should increase glucose oxidation in the failing human heart and skeletal muscle, and could decrease FFA- and hyperglycemia-associated oxidative stress. Of note, normalizing excess concentrations of reactive oxygen species counters pathways of hyperglycemic damage [27]. However, no trimetazidine-induced effect on cardiac glucose oxidation in human heart failure has yet been measured.

In summary, the major points in favor of the use of trimetazidine for heart failure are its simplicity of use, the benefit added to existing β-blockade, the

decreased insulin resistance, and the absence of any major adverse side effects.

Perhexiline for heart failure

Perhexiline is a partial inhibitor of fatty acid oxidation, inhibiting the mitochondrial uptake of FFAs that is catalyzed by the enzyme carnitine palmityltransferase-1 – which differs from the proposed site of action of trimetazidine. It requires monitoring of blood concentrations to avoid liver or neural toxicity. In the only study of perhexiline in heart failure, when the drug was added to the existing therapy, peak exercise-induced oxygen uptake, quality of life, and left ventricular ejection fraction were all improved [28]. Perhexiline also normalized the post-exercise recovery of phosphocreatine in skeletal muscle. Although, to date, that remains the only detailed study of this drug in heart failure, the concordance of the findings with basic science studies and the unique mechanism of action of perhexiline on one mitochondrial enzyme are in contrast to the many diverse effects reported for trimetazidine. Note, however, that there is, as yet, no proof that perhexiline inhibits cardiac FFA oxidation in human heart failure, which remains an inferential mechanism of action.

Ranolazine for heart failure

Ranolazine, an agent that structurally resembles trimetazidine, is registered for use in angina of effort in the USA. It was originally regarded as having metabolic effects consonant with the benefits of a shift from fatty acid to glucose metabolism, as found in ischemic rat hearts. In patients with chronic angina and diabetes [29] or with acute coronary syndrome [30], there is improved glycemic control, with a persistent decrease in glycated hemoglobin concentrations, which would agree with the decreased insulin resistance found in the trimetazidine studies. The current suggestion is that ranolazine inhibits the late sodium inward current. Sodium overload may be responsible for a secondary calcium overload by subsequent sodium–calcium exchange, a hypothesis that requires further testing and studies in humans.

Summary

In DCM, the diseased myocardium causes the size of the myocardial cavity to enlarge, thereby increasing wall tension. In hypertrophic cardiomyopathy, the cause of the hypertrophy is genetic. The extreme degree of hypertrophy sensitizes the myocardium to a series of abnormalities that eventually cause myocardial fibrosis and, thereby, myocardial failure. The most common cause of cardiomyopathy secondary to pre-existing disease is that resulting from coronary artery disease complicated by myocardial infarction. Before diagnosing primary cardiomyopathy, which is myocardial disease of truly unknown cause, other diseases that must also be excluded are endocrine disorders, anticancer drugs, alcohol, and nutritional disorders; latent virus infection may be difficult to exclude. As investigations become more and more sophisticated, the diagnosis of primary idiopathic cardiomyopathy of unknown cause becomes less and less frequent.

From the point of view of treatment of heart failure caused by cardiomyopathy, any underlying cause must be addressed, while the heart failure is managed by standard therapy with diuretics as needed, chronic ACE inhibition (often with aldosterone blockade), and titrated doses of β-blockade. This paper has argued for the addition of metabolic therapy, the best tested example of which in humans is trimetazidine, with its ultimate extracardiac effect being on insulin resistance; perhexiline has only one study in human heart failure in its favor, and ranolazine none to date. Theoretically, each of these agents works on a different molecular site; ultimately, their use in combination should be possible, in order to achieve maximal metabolic benefits. ■

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